A phase I, open-label, multicenter study to assess the safety, pharmacokinetics and preliminary anti-tumor activity of AZD4635 both as monotherapy and in combination in patients with advanced solid malignancies: results from prostate cancer patients (NCT02740985)

Emerson Lim[1], Todd Bauer[2], Manish Patel[3], Gerald Falchook[4], Janet L Karlix[5], Jennifer Choe[6], Dan George[6], Ganesh Mugundu[7], Elizabeth Pilling[8], Huifang Chen[7], Bolan Linghu[7], Lara McGrath[7], Wenlin Shao[7], Melinda S. Merchant[7], Ben Sidders[8], Kris Sachsenmeier[7], Gayle P Pouliot[7], Charles G Drake[1], Johanna Bendell[2]

Columbia University Herbert Irving Comprehensive Cancer Center, New York, NY[1]; Sarah Cannon Research Institute/Tennessee Oncology[2], Nashville, TN; Sarah Cannon Research Institute/Florida Cancer Specialists, Sarasota, FL[3]; Sarah Cannon Research Institute/ HealthONE, Denver, CO[4]; Sara Cannon Development Innovations, Nashville, TN[5]; Duke Cancer Institute, Durham, NC[6]; AstraZeneca, Waltham, MA[7]; AstraZeneca, Cambridge, UK[8].

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Introduction

- Adenosine in the tumor microenvironment plays an important role in innate and adaptive immunity affecting immune function.
- Pharmacologic blockade of signaling through the adenosine 2a receptor (A2aR) may counteract the immunosuppressive effects of adenosine and allow for a more robust anti-tumor immune response in combination with immune checkpoint inhibitors.
- AZD4635 is an oral inhibitor of A2aR signaling and has been shown in preclinical models to increase dendritic cell activation, antigen presentation and cytotoxic T cells.
- This phase I study assessed the safety, pharmacokinetics, pharmacodynamics and efficacy of AZD4635 monotherapy (mono) and in combination (combo) with durvalumab (Imfinzi) in patients with refractory solid tumors.
- Here we present data for immune checkpoint-naïve pts with metastatic castrate-resistant prostate cancer (mCRPC).

Methods

- This multicenter phase 1 study enrolled patients with refractory solid tumors including metastatic castrate resistant prostate cancer and is still ongoing at the time of the DCO of 2 Dec 2019.
- Patients with refractory mCRPC received AZD4635 monotherapy (75 mg or 100 mg QD oral nanosuspension or 75 mg capsule (Mono) or in combination (75 mg or 100mg QD) with durva 1.5g IV q4wk (Combo).
- Peripheral blood was analyzed for TCR sequencing and samples were also analyzed for gene expression (Nanostring).
- ctDNA (Guardant OMNI) in plasma samples were sequenced in a subset of these patients.

Results

Table 1 Baseline mCRPC Patient Demographics and Clinical Characteristics

	Mono(N=56)	Combo(N=43)
Age, Mean (range)	71.3y (40-88)	70.1y (52-82)
ECOG, PS 0/1/2, n (%)	19 (34%)/ 37 (66%)/ 0	15 (35%)/ 27 (63%)/ 1 (2%)
Site of Disease, n (%)		
Bone	53 (95%)	34 (79%)
Local LN / distant LN	16 (29%) / 23 (41%)	20 (47%) / 28 (65%)
Lung	9 (16%)	8 (19%)
Liver	7 (13%)	10 (23%)
Other	15 (27%)	12 (28%)
Prior Regimens, med (range)	5 (2-10)	5 (1-10)
Prior Chemo, n (%)	34 (61%)	26 (61%)
Prior Hormonal Tx, n (%)	56 (100%)	41 (95%)
Prior NHA	52 (93%)	38 (88%)

Table 2 Causally-related AEs in >10% of mCRPC IO-naïve Patients

	Number (%) of patients			
	Mono (N=56)		Combo (N=43)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Nausea	39(69.6)	1(1.8)	28(65.1)	2(4.7)
Fatigue	16(28.6)	1(1.8)	9(20.9)	0
Vomiting	13(23.2)	1(1.8)	9(20.9)	0
Decreased Appetite	8(14.3)	0	12(27.9)	0
Dizziness	9(16.1)	0	8 (18.6)	1(2.3)
Diarrhea	8(14.3)	0	3(7.0)	0

- Immune-mediated adverse events were in line with what has been reported for durvalumab monotherapy [1].

PK data at 100 mg above the in vitro IC50

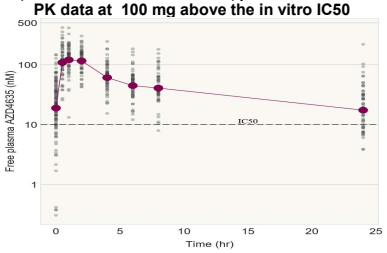


Figure 1. PK data suggest AZD4635 concentrations at 100 mg QD are above the *in vitro* IC_{50} for A2aR inhibition throughout the dosing interval. Modeling predicts 80-90% A2aR occupancy at steady state for doses at ≥75 mg QD (Data not shown).

PSA responses were seen for mono and combo-treated pts

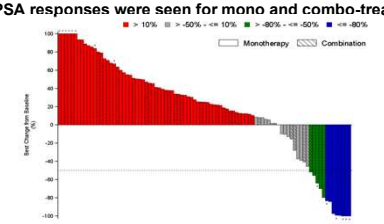


Figure 2. PSA responses were seen for a greater proportion of combination than monotherapy-treated patients.

Table 3 RECIST & PSA Response

BOR[1] n(%)	Mono(N=36)	Combo (N=37)
CR/PR	2 (5.6%)	6 (16.2%)
SD	13 (36.1%)	18 (48.6%)
PD	13 (36.1%)	11 (29.7%)
NE	8 (22.2%)	2 (5.4%)
PSA response[2]	3/51 (5.9%)	10/45 (22.2%)

[1] Based on dosed patients with measurable disease at baseline.
[2]PSA response defined as ≥50% reduction from baseline. Based on dosed patients with an abnormal baseline PSA (≥1ng/mL).

Clinical Activity in mCRPC IO-naïve Patients Treated With AZD4635 + durvalumab

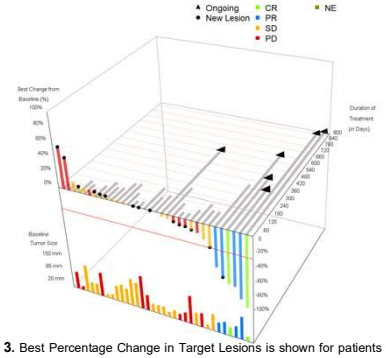


Figure 3. Best Percentage Change in Target Lesions is shown for patients treated with AZD4635+ durva with best objective response coded by color and duration of treatment on the z axis. Duration of response ranged from 2.3-25.8 mo at the DCO with several patients ongoing as indicated above.

Adenosine Signature Predicts PFS in mCRPC patients

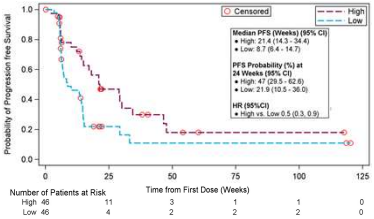


Figure 4. A retrospective analysis of PFS using an independently derived adenosine expression signature[2] predicted for patients with prolonged PFS. Patients treated with either monotherapy or combination with durvalumab were included. Median PFS in unselected population was 13.6 wks for monotherapy v. 14.9 weeks for combination with durvalumab (data not shown). Kaplan-Meier method and Cox model were used.

Exploratory Biomarkers Associated With PFS on AZD4635

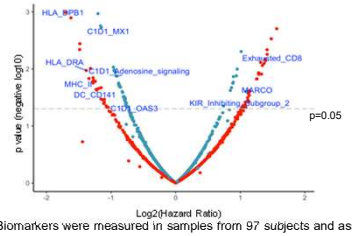


Figure 5. Biomarkers were measured in samples from 97 subjects and association with PFS was assessed using a log-rank test. Biomarkers included baseline (C1D1, blue circles) and pharmacodynamic changes (log2 fold-change between C1D1 and C1D15, red circles) in whole blood levels of gene expression and TCR sequencing as well as baseline lab chemistry. A volcano plot of log2 hazard ratio vs the negative log 10 nominal p value (dotted gray line) is plotted as in Li [4]. Following correction for false discovery rate (FDR) no features achieved significance.

TCR Repertoire Features Associated With AZD4635 Response

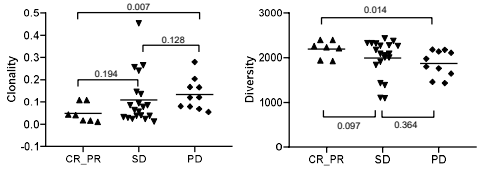


Figure 6. Baseline (C1D1) blood samples from 37 subjects with evaluable data were taken prior to treatment with AZD4635 alone or in combination with durvalumab. T cell receptor (TCR) repertoire analysis was performed on extracted DNA and measures of clonality (Fig. 5A) and diversity (Fig. 5B) are plotted for each class of best overall response by RECIST. Numbers indicate p values from a Mann-Whitney (Clonality) and Welch-corrected T-Test (Diversity).

Exploratory ctDNA Evidence Informing AZD4635 Resistance

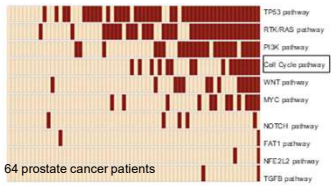
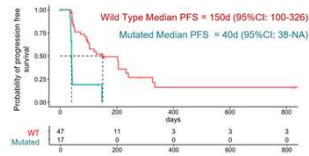


Figure 7A. Baseline ctDNA sequencing of 64 subjects subsequently treated with AZD4635 alone (n= 32) or in combination with durvalumab (n= 32) was analyzed for the number of pathways altered[3].

Figure 7B. By log-rank test, subjects with alterations within various cell cycle pathway genes showed significantly lower PFS by retrospective analysis. Curves were estimated using the Kaplan-Meier method.



Conclusions

- In mCRPC patients, AZD4635 alone or in combination with durvalumab was tolerable and associated with clinical benefit.
- Retrospective analysis of PFS shows clinical benefit is associated with high adenosine (ADO) gene expression signature in peripheral blood.
- Analysis of patient peripheral blood provides evidence of immune activation.
- Additional exploratory analysis of ctDNA demonstrated several key altered pathways which suggest potential combination strategies.
- Additional studies ongoing for AZD4635 in mCRPC and other tumor types

References:

1. Durvalumab Prescribing Information.
2. Sidders et al, *CCR* 2020.
3. Sanchez-Vega and Armenia et al, *Cell* 2018
4. Li et al, *Biological Research* 2018

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